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Registration Decision RD2015-08

Bacillus thuringiensis subsp. *aizawai* strain ABTS-1857

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Registration Decision for *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is granting full registration for the sale and use of XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide, containing the technical grade active ingredient *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857, to control many Lepidoptera larvae that are pests of various fruit, vegetable, oilseed and ornamental crops.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

These products were first proposed for registration in the consultation document[1] Proposed Registration Decision PRD2014-17, Bacillus thuringiensis *subsp.* aizawai *strain ABTS-1857.* This Registration Decision[2] describes this stage of the PMRA's regulatory process for *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 and summarizes the Agency's decision, the reasons for it and provides, in Appendix I, a summary of comments received during the consultation process as well as the PMRA's response to these comments. This decision is consistent with the proposed registration decision stated in PRD2014-17.

For more details on the information presented in this Registration Decision, please refer to PRD2014-17, which contains a detailed evaluation of the information submitted in support of this registration.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[3] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its conditions of registration. The Act also requires that products have value[4] when used according to label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in

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1 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

2 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

3 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

4 "Value" as defined by subsection 2(1) of the *Pest Control Products Act* "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact".

humans (for example, children) as well as organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management section of Health Canada's website.

What is *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857?

Bacillus thuringiensis subsp. *aizawai* strain ABTS-1857 is a bacterium found naturally in soil. Fermentation solids, spores and insecticidal toxins from the culturing of this bacterium are used to formulate XenTari WG Biological Insecticide. The insecticidal toxins produced by *Bacillus thuringiensis* bacteria are proteins that bind to specific receptors on insect gut cells and then disrupt the membranes of the gut cells. This disruption of the gut cells causes the insect to stop feeding and allows germinating spores of the bacterium to invade and cause a fatal infection in the insect. The protein toxins produced by the subspecies *aizawai* are specific to the larvae of insects in the order Lepidoptera, many of which are pests of food and ornamental crops. Due to the nature of its mode of action, XenTari WG Biological Insecticide must be eaten by the target pests in order to be effective.

Health Considerations

Can Approved Uses of *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 Affect Human Health?

Bacillus thuringiensis subsp. _aizawai_ strain ABTS-1857 is unlikely to affect your health when XenTari WG Biological Insecticide is used according to the label directions.

People could be exposed to *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 when handling and applying XenTari WG Biological Insecticide and when ingesting treated produce. When assessing health risks, several key factors are considered:

- the microorganism's biological properties (for example, production of toxic by-products);
- reports of any adverse incidents;
- the microorganism's potential to cause disease or toxicity as determined in toxicological studies; and
- the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

Toxicological studies in laboratory animals describe potential health effects from large doses in order to identify any potential pathogenicity, infectivity and toxicity concerns. When XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide were tested on laboratory animals, there were no signs that it caused any significant toxicity or disease. Besides the microorganism, soy lecithin present in the end-use product is known to be an allergen and must be labelled as such.

Residues in Water and Food

Dietary risks from food and water are not of concern.

As part of the assessment process prior to the registration of a pesticide, Health Canada must determine whether the consumption of the maximum amount of residues, which are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. The maximum amount of residues expected is then legally established as a maximum residue limit (MRL) under the *Pest Control Products Act* for the purposes of the adulteration provision of the *Food and Drugs Act*. Health Canada sets science-based MRLs to ensure that the food Canadians eat is safe.

Bacillus thuringiensis subsp. *aizawai* is a ubiquitous bacterium that is commonly found in soil and phylloplane. When XenTari Biological Insecticide Technical Powder and XenTari WG Biological Insecticide, which contain *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 as the active ingredient, were administered orally to rats, no signs of toxicity or disease were observed, and no metabolites of toxicological significance have been shown to be produced by this strain of *B. thuringiensis* subsp. *aizawai*. Also, no adverse effects were reported for this microorganism in the United States where it has been registered since 1992. Therefore, the establishment of an MRL is not required for *B. thuringiensis* subsp. *aizawai* strain ABTS-1857. As well, the likelihood of residues contaminating drinking water supplies is negligible to non-existent. Consequently, dietary risks are minimal to non-existent.

Risks in Residential and Other Non-Occupational Environments

XenTari WG Biological Insecticide is for use only in agricultural settings. No residential uses were requested. The product application directions on the label include statements to minimize spray drift. Thus, exposure health risks for bystanders in these environments are expected to be negligible.

Occupational Risks From Handling XenTari WG Biological Insecticide

Occupational risks are not of concern when XenTari WG Biological Insecticide is used according to label directions, which include protective measures.

Workers handling XenTari WG Biological Insecticide can come into direct contact with *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 on the skin, in the eyes or by inhalation. For this reason, the product label will specify that workers exposed to XenTari WG Biological Insecticide must wear waterproof gloves, long-sleeved shirts, long pants, a dust/mist filtering respirator/mask (NIOSH approval number prefix TC-21) or NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter) and shoes plus socks. Eye goggles are not required as the eye irritation studies submitted indicated minimal eye irritation potential.

For the bystander, exposure is expected to be much less than that of handlers and mixer/loaders and is considered negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When XenTari WG Biological Insecticide Is Introduced Into the Environment?

Environmental risks are not of concern.

Bacillus thuringiensis spores are commonly isolated from terrestrial environments and are part of the soil micro-flora. Information available in the published literature on the environmental fate of *B. thuringiensis* spores and crystal proteins suggests some viable spores are expected to survive following application of XenTari WG Biological Insecticide to field crops. These can remain inactive and immobile in soil for several months or years with a gradual decline in spore viability.

XenTari WG Biological Insecticide is not intended for aquatic uses and exposure to aquatic environments is limited to spray drift and run-off (following a rain event) from field applications. The limited survival of *B. thuringiensis* spores in water is influenced by a complex interaction of a number of biological, chemical and physical factors.

Several trials were conducted to determine the effects of XenTari Biological Insecticide Technical Powder on birds, fish, bees, terrestrial and aquatic arthropods and terrestrial non-arthropod invertebrates. These studies showed that XenTari Biological Insecticide Technical Powder was not toxic or pathogenic to birds, fish, or plants. XenTari Biological Insecticide Technical Powder was toxic and/or pathogenic to bees, certain beneficial insects and aquatic arthropods.

Although aquatic non-arthropod invertebrate and terrestrial plants toxicity/pathogenicity testing was not conducted, adequate information was available to determine that no significant adverse effects to these non-target organisms are expected.

Value Considerations

What Is the Value of XenTari WG Biological Insecticide?

Applied as a broadcast foliar spray, XenTari WG Biological Insecticide provides selective control of many Lepidoptera larvae that are pests of various fruit, vegetable, oilseed and ornamental crops.

XenTari WG Biological Insecticide has value for the control of various Lepidoptera pests such as codling moth, leafrollers, cabbage looper, leek moth and grape berry moth on apples, pears, broccoli, cabbage, cauliflower, Chinese cabbage, bok choy, Chinese broccoli, Asian radish, grapes, hops, tomato, pepper, eggplant, leek, artichoke and canola, and on greenhouse tomato, pepper, eggplant, cucumber, lettuce and beans, and greenhouse ornamentals.

XenTari WG Biological Insecticide has value as an alternative for the supported uses, some of which have few or no registered alternatives, and a few of which include alternatives that are being phased out. The product should be well suited to integrated pest management (IPM) due to its specificity for larvae of Lepidoptera and may be suitable for organic production. Registration in Canada would reduce a technology gap with the United States and would address several high priorities listed in the Canadian Grower Priority Database.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of XenTari WG Biological Insecticide to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

For individuals exposed to large quantities of XenTari WG Biological Insecticide, respiratory and dermal sensitivity could possibly develop upon repeated exposure to the product since all microorganisms, including *B. thuringiensis* subsp. *aizawai* strain ABTS-1857, contain substances that are potential sensitizers. Therefore, anyone handling or applying XenTari WG Biological Insecticide must wear appropriate waterproof gloves, a long-sleeved shirt, long pants, a dust/mist filtering respirator/mask (NIOSH approval number prefix TC-21) or NIOSH approved respirators (with any N-95, P-95, R-95 or HE filter) and shoes plus socks.

Environment

The end-use product label will include environmental precaution statements that prevent the contamination of aquatic systems from the use of XenTari WG Biological Insecticide, as well as statements indicating that XenTari WG Biological Insecticide is toxic and/or pathogenic to bees, certain beneficial insects and aquatic organisms.

Other Information

The relevant test data on which the decision is based (as referenced in PRD2014-17) are available for public inspection, upon application, in the PMRA Reading Room (located in Ottawa). For more information, please contact the PMRA Pest Management Information Service by phone (1-800-267-6315) or by e-mail (pmra.infoserv@hc-sc.gc.ca).

Any person may file a notice of objection[5] regarding this registration decision within 60 days from the date of publication of this Registration Decision. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticide and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act*.

Appendix I Comments and Responses

Consideration of additions and changes to the list of supported uses

1. A comment was made requesting that several uses and crops be added to the approved label before the final registration decision in order to be reflective of the needs identified by Canadian producers.

Response
The PMRA wishes to indicate that all the crops proposed for registration by the applicant have been supported. Requests for use expansions and User Requested Minor Use Label Expansions should be submitted as new applications to amend the existing registration.

Registration Decision on Bees

2. A comment indicated that the mean test substance consumption values for honeybees (Section 4.2.1 Effects on Terrestrial Organisms) needed to be corrected to describe the actual amount of test substance consumed/day in the test. The suggestion was to change the values shown in bold font: "*The mean consumption values for honeybees fed 1000, 100, 10 and 1 ppm XenTari Biological Insecticide Technical Powder were **54, 48, 49, and 51 mg/bee/day**, respectively.*" to: "*0.054, 0.0048, 0.00049, and 0.000051 mg bee/day*".

Response
The feed suspensions contained honey, water and either 1000, 100, 10, or 1 ppm Xentari Biological Technical Powder. The values "*54, 48, 49, and 51 mg bee/day*" reported in PRD2014-17 refer to the mean quantity of feed suspension consumed per bee per day. The values in the comment (0.054, 0.0048, 0.00049, and 0.000051 mg/bee/day) are referring only to the amount of active ingredient (Xentari Biological Technical Powder) that was consumed per bee per day. No correction is necessary since both sets of values are different but accurate.

3. According to a comment received, laboratory studies are normally conducted to determine the LD_{50} of the material and are conducted for only a two-day duration. The usual test duration is 48 h and can be prolonged up to 72 h or 96 h if mortality is increasing between 24/48 h or 48/72 h. The commenter noted that current guideline conditions invalidate studies where mortality in control groups is over 10%. There was a greater than 10% mortality in the control group already at day 8, indicating the bees were already in poor condition. The study of continuous feeding of these rates of *B. thuringiensis* strain ABTS-1857 was also stated as being unrealistic as it does not take into account the degradation of the microbe that would occur naturally in nature.

Response
PMRA's Regulatory Directive, DIR2001-02 *Guideline for the Registration of Microbial Pest Control Agents and Products* states the following: "For Tier I exposure or dietary tests, non-target arthropods should be exposed to, or fed the maximum challenge concentration (MCC) of the microbial pest control product (MPCA) or the end-use product for at least 21 days, or until mortality in the control group increases to a significant level."

A test duration of 21 days is necessary so that effects due to pathogenicity may be observed. The study referred to as PMRA reference 2259602 showed that bees exhibited a consistent dose-mortality response from dietary exposure to the test substance indicating that *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 is toxic and/or pathogenic to the honeybee via the dietary route of exposure.

4. According to a comment, the number of applications of the product during the four-week toxicity/pathogenicity study (Section 4.2.1 Effects on Terrestrial Organisms) should have been taken into account as a sufficient challenge (dosing regime) to the treatment group hives.

Response
In the honeybee four-week toxicity/pathogenicity study conducted on hives, it can be concluded that no contact toxicity/pathogenicity occurred. However, dietary toxicity/pathogenicity to the honeybee could not be assessed due to the lack of statistical power of the study (that is, adverse effects may have occurred but could not be observed due to the highly variable nature of the data) and XenTari WG Biological Insecticide was applied only to the interior surfaces of the hive. The dietary exposure in this study is expected to have been minimal relative to the dietary exposure expected from bees foraging on treated crops. It is noted that *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857 is toxic and/or pathogenic via the dietary route (as seen in PMRA reference 2259602) and that the mode of action of the MPCA to target insects is via the dietary route. This study does not address the hazard to bees from foraging on crops treated with *Bacillus thuringiensis* subsp. *aizawai* strain ABTS-1857.

5. A comment cited the following paragraph from PRD2014-17:

"Based on all the available data and information on the effects of *B. thuringiensis* subsp. *aizawai* strain ABTS-1857 to non-target terrestrial organisms, and the precautionary measures required on the XenTari WG Biological Insecticide label, there is reasonable certainty that no harm will be caused to birds, wild mammals, arthropods (including honeybees), non-arthropod invertebrates, and plants from the proposed use of XenTari WG Biological Insecticide."

The comment also stated that the above cited text parallels the conclusions drawn by the European Union Commission (taken from the European Food Safety Authority [EFSA] conclusion) as follows:

"Conclusion on the peer review of the pesticide risk assessment of the active substance *Bacillus thuringiensis* subsp. *aizawai* (strains ABTS 1857, GC-91). EFSA Journal 2013;11(1):3063 [49 pp.]

Bacillus thuringiensis aizawai strain ABTS-1857 was chronically pathogenic and toxic to honeybees when continuously fed at high dosages over 9-12 days under laboratory conditions. However, a higher tier study on *Apis mellifera* indicated no significant effects between the control and the treatment groups with regard to adult mortality, population changes, or queen survival. No toxicity effects were observed in a study with bumblebees. Therefore, the risk for bees was concluded as low for the representative uses of strain ABTS-1857."

In conclusion, the comment is requesting that the following Environment Hazard label language be reconsidered:

"ENVIRONMENTAL HAZARDS

Toxic to bees. Bees may be exposed to direct treatment, drift, or residues on flowering crops or weeds. DO NOT apply this product to flowering crops if bees are visiting the treatment area. Minimize spray drift to reduce harmful effects on bees in habitats close to the application site. Toxic to certain beneficial insects. Minimize spray drift to reduce harmful effects on beneficial insects in habitats next to the application site such as hedgerows and woodland.

This product is toxic to aquatic organisms."

Response
The PMRA notes that the concluding statements from the European Commission do not include a requirement for precautionary measures, as pertains to bees, to appear on the label and therefore differs from the PMRA conclusion in that regard. The PMRA has reconsidered the label language under the heading Environmental Hazards and has determined that no changes are necessary as they are appropriate for the protection of non-target insects including bees and other pollinators.

6. A comment requested clarification as to why the bumblebee study was not considered for the risk assessment.

Response
The PMRA wishes to clarify that the bumblebee study was reviewed and found to be unacceptable since a critical detail, the identity of the material tested, was not adequately described and the study was not conducted according to Good Laboratory Practices.